PB81-233827

Preliminary Report on Nationwide Study of Drinking Water and Cardiovascular Diseases

(U.S.) Health Effects Research Lab.
Cincinnati, OH

Jul 81

U.S. Department of Commerce
National Technical Information Service

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1. REPORT NO.	2.	3. RECI
EPA-600/J-80-297	Journal Article	PB81-233827

4. TITLE AND SUBTITLE	5. REPORT DATE
Preliminary Report on Nationwide Study of Drinking Water and Cardiovascular Diseases	July 1981
	6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)	8. PERFORMING ORGANIZATION REPORT NO.
Daniel G. Greathouse & Rebecca H. Osborne	
9. PERFORMING ORGANIZATION NAME AND ADDRESS	10. PROGRAM ELEMENT NO.
U.S. EPA Health Effects Research Laboratory 26 W. St. Clair St. Cincinnati, OH 45268	11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS	13. TYPE OF REPORT AND PERIOD COVERED
Same	14. SPONSORING AGENCY CODE

15. SUPPLEMENTARY NOTES

Published in: Journal of Environmental Pathology & Toxicology 4-2,3:65-76(Sept.1980)

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17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U.S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA 22161

18. DISTRIBUTION STATEMENT	19. SECURITY CLASS *(This Report)*	21. NO. OF PAGES
Release to Public	Unclassified	
	20. SECURITY CLASS *(This page)*	22. PRICE
	Unclassified	

EPA-600/J-80-297
Journal Article

PRELIMINARY REPORT ON NATIONWIDE STUDY OF DRINKING WATER AND CARDIOVASCULAR DISEASES

Daniel G. Greathouse, Rebecca H. Osborne

Health Effects Research Laboratory, U.S. Environmental Protection Agency, Cincinnati, OH 45202

This study was designed to further investigate the association(s) of cardiovascular diseases and drinking water constituents. A sample of 4200 adults were randomly selected from 35 geographic areas to represent the civilian noninstitutionalized population of the contiguous United States. Each participant was interviewed and given a thorough physical examination. A tap water grab sample was collected from each participant's residence and analyzed for 80 inorganic chemical constituents.

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INTRODUCTION

The study of the association(s) between inorganic constituents of drinking water and cardiovascular diseases began over 20 years ago. Enterline and Stewart (1956) suggested that place of residence might be considered a risk factor for cardiovascular disease. Kobayashi (1957) noted an association between water acidity and apoplexy mortality rates in Japan.

More recently, investigators have studied the association between the

Please send requests for reprints to Dr. Daniel G. Greathouse.

Journal of Environmental Pathology and Toxicology 4-2,3:65-76
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concentrations of inorganics in drinking water and cardiovascular diseases. In the extreme soft water areas in the U.S., cardiovascular mortality rates may be elevated by 15 percent over the cardiovascular mortality rates for hard water areas (Sharrett and Feinleib, 1974). Hard water may function in two ways in this effect on cardiovascular disease: it may contain inorganics that prevent cardiovascular disease or modify disease severity, or it may not contain inorganics that predispose an individual to cardiovascular disease or that enhances disease severity. Conversely, the increased cardiovascular disease mortality seen in soft water areas may be due to the presence of deleterious inorganics or the absence of beneficial inorganics. These hypotheses have resulted in studies of the association(s) between certain constituents of source water and cardiovascular mortality rates for the geographic areas served by these source waters. While calcium and magnesium are consistently negatively correlated with cardiovascular disease mortality rates, correlations of other elements with cardiovascular disease are inconsistent among studies (Sharrett and Feinleib, 1974).

The early studies of associations between cardiovascular diseases and drinking water constituents used levels of constituents in aggregate samples of water plant effluents or source water samples as exposure assessments. Thus, the inorganic concentrations reported in these studies may not actually represent the quantity of inorganics consumed by individuals living in the geographical areas being studied. In our study, inorganic intake from drinking water was estimated by measurement of constituent levels in individual home water samples. Individual health status information was collected for at least one adult resident of each sampled household.

This study was a cooperative effort by the U.S. Environmental Protection Agency's Health Effects Research Laboratory, Cincinnati; the National Heart, Lung and Blood Institute; and the National Center for Health Statistics to further investigate the association(s) or cardiovascular diseases and ingestion of inorganic drinking water constituents. The study began in July, 1974 and field work was essentially completed in December, 1975. Health data were collected from individuals aged 25 to 74 years with emphasis placed on cardiovascular diseases (Public Health Service, 1978). Because of the magnitude of the study and the water sampling program, chemical analyses were not completed until mid-1977.

MATERIALS AND METHODS

A sample of 4200 adults (aged 25 to 74 years) was selected by the U.S. Bureau of the Census to represent the civilian noninstitutionalized population of the contiguous United States, excluding those living on lands set aside for use by American Indians. Approximately 120 adults were selected from each of 35 geographic areas (Fig. 1, Table 7). Each participant was interviewed and given a thorough physical examination. The Bureau of Census, under contract to the National Center for Health Statistics (NCHS), was responsible for the design of the sampling plan, selection of the sample, and performance of the initial interviews. Physical examinations were conducted by the National Center for Health Statistics.

FIGURE 1. Map of 35 geographic areas included in study (NCHS stands for Hanes I augmentation survey).

Medical, demographic, smoking, and drinking water exposure information (Table 1) were collected during the household interviews. While at the residence, a tap water sample was collected and the home plumbing materials were noted. Following the interview each individual was given a thorough physical examination by physicians, nurses, and technicians at a specially equipped mobile health center. A number of indicators of, and risk factors for, cardiovascular diseases were measured (Table 1).

Based on a review of the literature, 28 trace elements and other water quality parameters were identified as potentially related to cardiovascular diseases (Na, K, Ca, Mg, As, Se, Si, F, NO_3, Li, V, Mn, Fe, Cu, Zn, Mo, Ag, I, Cr, Co, Ni, Cd, Pb, hardness, alkalinity, conductivity, pH, and TDS). Because of the need for very sensitive measurement of several trace inorganic elements in approximately 5000 samples, a multielemental analytic method for inorganic analysis was utilized. The Proton Induced X-ray Emission (PIXE) multielemental technique was selected because of its broad range. Since the PIXE method is only useful for detection of elements heavier than Ca, more routine analytic procedures such as atomic absorption and wet chemistry were used for some of the elements.

A contract was awarded to Purdue University for the PIXE analyses. The analytic methodology is described in a published EPA report (Simms and Rickey, 1978).

TABLE 1. Information Collected from Each Participant

A. Information Collected During Initial Participant Interview
   1. Name of current water supplier and length of time used
   2. Use of water conditioners
   3. Residential plumbing pipe types
   4. Water consumption pattern
   5. Medical history

B. Cardiovascular Information Collected During Participant Physical Examinations
   1. Physician examination supplemented with a cardiovascular questionaire
   2. Multiple blood pressure measures
   3. Pulse rate
   4. Serum cholesterol and uric acid
   5. Chest x-ray

C. Water Chemistry Information
   A household tap water sample collected from each of 3854 participant residences and analyzed for approximately 80 inorganic constituents and characteristics.

The detection limits for the PIXE method were generally l ug/l or less for trace elements and 100 ug/l for bulk elements. However, the detection limits for an individual sample were altered somewhat by the level of calcium in the sample. Specifically, if the calcium concentration was less than or equal to 50 mg/l the specified detection limits were: (1) K:100 ug/l; (2) V, Mn, Fe, Cu, Zn, Mo, Ag:1.0 ug/l ; (3) Cr, Co, Ni, Cd, Pb:0.1 ug/l. For samples with greater than 50 mg/l of calcium, the detection limits were increased by the factor: (calcium concentration (mg/l) ÷ 50 mg/l).

In order to insure a high level of accuracy and precision, the contractor was required to: (1) periodically perform and report adequate calibrations for each of 35 key elements; (2) add an internal standard, yttrium, to each sample and calculate percent recovery for quality control purposes; (3) satisfactorily analyze blind duplicates of approximately 5 percent of the total number of water samples collected; (4) satisfactorily analyze preserved aqueous standards (developed by EPA, NBS, and the U.S. Geological Survey) which included 15 elements at various concentrations. Since the only analytic results presented in this paper are those from the PIXE methods, the detection limits and quality control measures for the other analytic methods are not included.

RESULTS AND DISCUSSION

Due to concerns that participant confidentiality be maintained, the household tap water samples were collected by the Bureau of the Census and relabelled with a secret code by the National Center for Health Statistics (NCHS) before giving them to the U.S. Environmental Protection Agency (U.S. EPA) for chemical analysis. The U.S. EPA supplied NCHS with the coded chemistry results for merging with the collected health and demographic data.

Since the NCHS has not yet released the merged data files, the subject of this paper is limited to discussion of the chemistry data and its relationship(s) to area-wide/specific cardiovascular mortality rates.

In order to determine if tap water quality is related to cardiovascular mortality rates for the 35 geographic areas, sex and race specific age-adjusted cardiovascular mortality rates (1968 - 1972) were regressed against the area means of a number of tap water constituents. Mortality rates for the age group 35 to 74 were age-adjusted by the direct method by 10 year age group to the total U.S. population in those age groups in 1950. The area means are the average of the specific constituent levels in the tap water samples collected from the (100-110) sampled households in the area; samples with a constituent level below the detection limit were assigned to a value equal to one-half of the detection limit. The particular elements selected for consideration in this paper are the ones that have received much attention in other similar studies during the past 20 years. Unweighted regression methods were used to analyze the data; since the variances of the mortality rates likely vary with population sizes, the analyses might have been improved by application of weighted regression methods.

It should be noted that regression of 1968 to 1972 mortality rates on mean levels of inorganic constituents in samples collected during 1974 to 1975 requires an assumption that the constituent levels have remained relatively constant over time. As in most ecologic studies of this type, it is also assumed that there are no significant differences in mobility, ethnicity, diet, etc. among the study areas.

Mean levels of water hardness ($CaCO_3$) calculated by $2.5(Ca^{2+})+4.1(mg^{+})$ have the characteristic negative association with all of the cardiovascular mortality rates (Table 2), except cerebrovascular disease. However, only one of the associations (cardiovascular-renal disease minus ischemic and cerebrovascular diseases for males) is statistically significant ($p=0.039$). Since some of the area means were more strongly associated with the death rates for total cardiovascular diseases than with the rates for ischemic or cerebrovascular diseases, the distribution of rates for nonischemic and noncerebrovascular deaths (primarily hypertensive and renal diseases) were examined. The range of mean hardness levels varied from 6.5 to 325 mg/l.

Based on the least squares line, areas with hard water (300 mg/l of $CaCO_3$) experience on the average 10.5 percent less male deaths from cardiovascular and renal disease than communities with soft water (20 mg/l of $CaCO_3$). However, since the slope of the regression line is not significantly different ($p=0.283$) from zero, there is insufficient evidence to reject the hypothesis that the actual difference may be equal to zero.

The associations for calcium are similar (in terms of direction and statistical significance) to those observed for hardness (Table 2).

The associations between average copper levels and cardiovascular diseases mortality rates are all positive (Table 2). Even though only two of the slopes are statistically significant (cardiovascular-renal and cardiovascular-renal minus ischemic and cerebrovascular for females), the direction of associations appears to be generally opposite that for hardness and calcium.

TABLE 2. Summary of Linear Regressions of Areawide, Age-Adjusted, Sex Specific Cardiovascular Mortality Rates (35 Geographic Areas) Against Mean Levels (by Area) of Specific Inorganic Constituents in One Time Grab Samples of Tap Water Collected from 100 to 120 Area Residences (Collected During 1974 and 1975)

		Cerebrovascular Disease (ICDA 430-438)				Cardiovascular-Renal Disease minus Ischemic and Cerebrovascular Disease (ICDA 390-404, 414-429, 440-458, 582-584)			
Water Constituents	Sex	Slope[1]	Intercept	R^2	Significance Level[1] P	Slope[1]	Intercept	R^2	Significance Level[1] P
Hardness ($CaCO_3$)	M	0.029	992.21	0.004	0.717	*-1.078*[1]	1186.75	0.123	*0.039*[1]
	F	0.242	726.90	0.019	0.429	-0.482	685.47	0.077	0.106
Calcium	M	0.824	987.71	0.008	0.603	*-3.17*[1]	1175.63	0.140	*0.027*[1]
	F	0.638	731.69	0.018	0.448	-1.47	682.04	0.094	0.073
Copper	M	127.26	996.60	0.004	0.708	317.40	1032.29	0.030	0.317
	F	197.59	725.20	0.037	0.2717	*346.43*[1]	588.71	0.114	*0.047*[1]
Zinc	M	251.91	956.63	0.073	0.094	91.11	1054.52	0.014	0.499
	F	*213.72*[1]	703.41	0.238	*0.003*[1]	35.59	627.47	0.007	0.640
Cadmium	M	-40,908.81	1039.32	0.009	0.581	-30,767.92	1094.40	0.006	0.659
	F	-7733.67	756.74	0.001	0.845	-50,510.63	667.06	0.051	0.193
Lead	M	-635.50	1017.85	0.002	0.943	6647.87	1032.87	0.020	0.424
	F	-832.16	757.21	0.001	0.861	*9219.78*[1]	576.84	0.118	*0.043*[1]
Sodium	M	*-1.65*	*1059.86*	*0.035*	*0.285*	*-1.04*	*1104.20*	*0.016*	*0.476*
	F	*-0.120*	*755.28*	*0.001*	*0.885*	*-0.671*	*654.31*	*0.021*	*0.412*

[1]Slopes that are statistically significant at $p<0.05$ are indicated by italics in the slope and significant level

Zinc appears to be negatively associated with the mortality rates for total cardiovascular diseases and ischemic disease but positively associated with deaths attributed to cerebrovascular disease and the other cardiovascular and renal diseases which are not classified as ischemic heart or cerebrovascular disease. However, from Table 3 it is apparent that most of the zinc values cluster below 236 ug/l and that the gradient of values is too small to adequately test the zinc associations.

TABLE 3. Distribution of Areawide (35) Mean Levels of the Inorganic Constituents in (100-110) Household Grab Samples

Water Constituent	Minimum[1]	25th Percentile[1]	Median[1]	75th Percentile	Maximum[1]
Hardness[2]	6.52	53.04	90.67	129.51	324.51
Calcium	1.89	13.95	25.57	41.50	120.60
Copper	0.010	0.032	0.092	0.232	0.420
Zinc	0.025	0.077	0.144	0.236	1.447
Cadmium	0.0002	0.0004	0.0004	0.0007	0.0029
Lead	0.002	0.003	0.005	0.007	0.018
Sodium	4.08	10.21	15.95	40.15	112.01

[1]Units are mg/l
[2]$CaCO_3$ calculated by 2.5 (C_3^{++}) + 4.1(Mg^{++})

Contrary to expectation, the associations of mean cadmium levels and cardiovascular disease mortality rates are consistently negative (Table 2). The mean cadmium levels ranged from approximately 0.2 ug/l to less than 3 ug/l. However, since all but 4 means were less than 1.0 ug/l, the significance of the slopes or their direction is questionable.

The range of area mean lead concentrations is narrow (<2 to 18 ug/l) but the levels are more variable than those observed for the cadmium and zinc. Hence, the direction and significance levels of the slopes are less subject to question than those for cadmium and zinc. The very significant positive slopes for female mortality rates (total cardiovascular-renal, ischemic heart, and total cardiovascular-renal minus ischemic heart and cerebrovascular) and similar directional but less significant relationships for males may indicate that lead contributes to cardiovascular disease mortality.

The consistently negative slopes for sodium for males and females in the four cardiovascular disease groups is surprising. Particularly so, since the slopes for total cardiovascular diseases and ischemic heart disease is significantly different from zero for both males and females. These negative relationships may be due to the use of water softeners in hardwater areas and/or to the fact that sodium occurs naturally at moderate levels in hardwater, or that something else in soft water-not sodium-is the culprit.

The statistically significant slopes for the tested associations provide indication of causal associations, but all should be considered in terms of the well known ecologic fallacy and the multiple comparison problem. Hence, the results of these analyses should only be used for comparison with other similar studies and to develop hypotheses for further testing.

Since inorganic constituents do occur singly in household tap water, Spearman correlations and associated significance levels (Table 4) were computed for the area mean levels of the seven parameters. Calcium and hardness are highly correlated (correlation coefficient × 0.990 with p=0.0001). One of the initial surprises is that sodium is significantly positively correlated with calcium and hardness. However, since many homes in hard water areas have individual home water softeners, it seems reasonable that the average sodium levels will be elevated by the homes with softener units and that the average hardness level will remain elevated because many residences don't have water softeners. Hence, area means for sodium and hardness, or calcium, would likely be correlated. The significant (p=0.003) positive correlation (correlation coefficient=0.488) for copper and lead seems reasonable since a major source of these elements is the household plumbing system in areas with corrosive waters. In the corrosive water areas, homes with copper plumbing will have elevated levels of copper in their water and homes with lead plumbing will have high levels of lead. Hence, in a corrosive water area high lead and copper would be expected. The significant cadmium associations with copper and lead may be real or statistical artifacts due to the small amount of variation in mean cadmium levels.

TABLE 4. Spearman (Nonparametric) Correlation Matrix of Mean Concentrations of Selected Inorganics in Sampled Tap Water for 35 Geographic Areas (Correlation Coefficient/Significance Level)

	Ca	$CaCO_3$	Cu	Zn	Cd	Pb	Na
Ca	1.00000	0.99020	-0.30588	0.12437	0.02941	-0.21064	0.52885
	0.00000	0.0001	0.0739	0.4766	0.8668	0.2245	0.0011
$CaCO_3$		1.00000	-0.30448	0.11793	0.03894	-0.17591	0.50952
		0.00000	0.0753	0.4999	0.8243	0.3121	0.0018
Cu			1.00000	0.34062	0.35462	0.48824	-0.27395
			0.00000	0.0453	0.0366	0.0029	0.1113
Zn				1.0000	0.30252	0.06134	-0.01429
				0.0000	0.0773	0.7263	0.9351
Cd					1.00000	0.38683	0.12325
					0.00000	0.0217	0.4806
Pb						1.00000	-0.22353
						0.00000	0.1968
Na							1.00000
							0.00000

As explained in the introduction, the primary purpose of this study was to investigate the associations of individual drinking water exposures and indicators, or measures, of cardiovascular health. One of the reasons for studying individuals is to improve the estimates of exposures to specific drinking water constituents. It seems unlikely that finished water samples from the water treatment plants are very representative of household tap waters which may be contaminated with inorganic chemicals from the plumbing or further treated with a home water conditioning unit. As an initial estimate of the relative variability of inorganic constituents for individual homes versus among geographic areas, a nested one-way analysis of variance technique was run for the basic elements (Table 5). Clearly the variation within areas is much greater than that among areas indicating that individual exposure assessments are definitely needed.

To avoid the phenomenon discussed for area correlations where some homes have high levels of one constituent and others have high levels of another constituent, Spearman correlations were computed for the basic elements in individual home samples (Table 6). Notice that sodium and calcium are still significantly positively correlated, but the correlation is not as strong as that for area means with the Spearman Rank Correlation Coefficient dropping from 0.529 to 0.248. This change in levels is probably due to the use of home water softeners which replace calcium ions with sodium ions. The remaining significant correlations may be due in part to the natural occurrence of higher sodium levels in hard water areas. Clearly a number of elements are significantly correlated within individual home samples, so that the effects of combinations of elements, rather than single elements needs to be considered.

TABLE 5. Percent of the Total Variation in Trace Metal Concentrations of Tap Water Samples Collected from 35 Geographic Areas Partitioned into within and between Area Differences as Determined by One Way Variance Components Analysis of Variance

		Trace Elements						
		$CaCO_3$	Ca	Cu	Zn	Cd	Pb	Na
Percent of Total Variation	Within Areas	60.75	61.69	94.72	93.30	99.80	94.38	76.46
	Between Areas	39.25	38.31	5.28	6.70	0.20	5.62	23.54
	TOTAL	100.00	100.00	100.00	100.00	100.00	100.00	100.00

TABLE 6. Spearman (Nonparametric) Correlation matrix of Concentrations of Selected Inorganic Chemical Constituents in Individual Tap Water Samples Collected from 35 Geographic Areas (Correlation Coefficient/Significance Level) (No. of Sample Results Included in Each Correlation Ranged from 3713 to 4220)

	Ca	Cu	Zn	Cd	Pb	Na
Ca	1.000	-0.0375	0.1210	0.1492	-0.1116	0.2484
		0.0198	0.0001	0.0001	0.0001	0.0001
Cu		1.0000	0.3611	0.2758	0.4892	-0.0630
			0.0001	0.0001	0.0001	0.0001
Zn			1.0000	0.3159	0.2566	-0.0470
				0.0001	0.0001	0.0035
Cd				1.0000	0.2195	-0.0681
					0.0001	0.0001
Pb					1.0000	-0.0308
						0.0556
Na						1.0000

TABLE 7. Study Areas for Health Examination Survey Cycle

Study Area	County	State	Study Area	County	State
1	Warren	New York	8	Platte	Missouri
2	Montgomery	Ohio		Clay	Missouri
	Greene	Ohio		Cass	Missouri
	Miami	Ohio		Jackson	Missouri
3	Middlesex	Connecticut		Wyandotte	Kansas
	New Haven	Connecticut	9	Caliborne	Tennessee
4	Rusk	Wisconsin		Hamblen	Tennessee
5	Essex	Massachusetts		Hancock	Tennessee
	Middlesex	Massachusetts		Hawkins	Tennessee
	Norfolk	Massachusetts	10	Hunt	Texas
	Plymouth	Massachusetts		Rains	Texas
	Suffolk	Massachusetts	11	Greenville	South Carolina
6	Marion	Indiana	12	Los Angeles	California
7	Essex	New Jersey		Orange	California
	Morris	New Jersey	13	Jefferson	Alabama
	Union	New Jersey	14	Sacramento	California
	Somerset	New Jersey	15	Volusia	Florida
	Hudson	New Jersey			
	Middlesex	New Jersey			

TABLE 7. Study Areas for Health Examination Survey Cycle

Study Area	County	State	Study Area	County	State
16	Alameda	California	25	Blair	Pennsylvania
	Contra-Costa	California	26	Jefferson	Kansas
	Marin	California		Leavenworth	Kansas
	San Francisco	California	27	Monroe	New York
	San Mateo	California	28	Jackson	Michigan
	Solano	California	29	Brown	Ohio
17	Jefferson	Louisiana		Clinton	Ohio
	Orleans	Louisiana	30	Cook	Illinois
	St. Bernard	Louisiana		Will	Illinois
18	Mason	Washington		Lake	Indiana
	Thurston	Washington		Porter	Indiana
19	Edgefield	South Carolina	31	Macomb	Michigan
	Saluda	South Carolina		Oakland	Michigan
20	Adams	Colorado		Wayne	Michigan
	Arapahoe	Colorado	32	Western Philadelphia	Pennsylvania
	Denver	Colorado		Bucks	Pennsylvania
	Jefferson	Colorado		Chester	Pennsylvania
	Boulder	Colorado		Deleware	Pennsylvania
21	New Castle	Deleware		Montgomery	Pennsylvania
22	Canadian	Oklahoma	33	Nassau	New York
	Cleveland	Oklahoma		Queens	New York
	Oklahoma	Oklahoma		Suffold	New York
23	Allegheny	Pennsylvania	34	Calhoun	West Virginia
	Beaver	Pennsylvania		Clay	West Virginia
	Washington	Pennsylvania		Roane	West Virginia
	Westmoreland	Pennsylvania	35	Bronx	New York
24	Greeley	Nebraska		New York	New York
	Nance	Nebraska			

From this preliminary analysis, some previously identified associations between trace elements and cardiovascular diseases have been re-affirmed and some new ones identified. These results will be used to guide future research efforts and to direct the analyses of the individual data when received from the National Center for Health Statistics. Future plans for this particular research study include evaluation of the health implications of drinking water contituents for blood pressure and hypertension, serum cholesterol, diagnosed cardiovascular conditions (CHD, ECG abnormalities, and diabetes), and bone density and arthritis. Metal pickup in the distribution system and seasonal variability in source trace elements will be further analyzed and evaluated.

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